Recent developments in chitosan encapsulation of various active ingredients for multifunctional applications

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Running head: *Chitosan encapsulation for multifunctional applications*

Abstract

Microencapsulation being an emerging technique has provided effective solution to the challenges faced by pharmaceutical, cosmetic, food agriculture and textile industries to deliver ingredients in their active forms to the target sites. Chitosan is a non-toxic, biodegradable and biocompatible amino polysaccharide which makes it useful for the encapsulation of various active ingredients with positive potential applications. Chitosan coating on food products, for example, gives them protection from possible antimicrobial attacks, antioxidants and extended shelf life. Likewise, its coating on pharmaceutics has valuable applications in preservation dn targeted drug delivery. In this review, we discuss the formation of chitosan, its properties, microencapsulation process, micro-capsular morphologies, selection of core and shell materials in addition to the process of chitosan encapsulation of various active ingredients and their applications in various fields of science and technology.

Keywords: Chitosan; Core; Encapsulation; Microencapsulation; Shell

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1 Introduction

The applications of natural products are widespread in food, cosmetics, perfumes and pharmaceutical industries. Many natural products are also used in textiles to improve the textures of fibrous materials for multipurpose applications. Chitosan (deacetylated chitin) is such a

product, typically found in exoskeletons of arthropods and crustaceans and also in fungal cell walls. It is a polycationic polysaccaride compound which has a tendency to interact with other chemicals resulting in various novel morphologies of microcapsules. The rigid chemical structure of chitosan makes it suitable in forming films, gels and microcapsules. Moreover, its biological, chemical and physical properties make it viable for developing the microcapsules containing active ingredients [1].

A microcapsule comprises of a core and a shell matrix, the core contains active ingredient whereas the shell is either a polymeric or a waxy material. The preparation of microcapsules depends on various parameters such as solubility, viscosity and the emulsification behaviour of the reaction mixture. Once applied on a desirable site, the active ingredients are inclined to be released under controlled conditions. The shell behaves as a transferring channel to the target where it releases the active ingredients which in turn depend on the material used for the shell formation including its specific end uses [2]. Microencapsulation allows the control release of the active ingredient for deposition at targeted site under specific conditions to carry out the required functionality. Any external chemical, physical or mechanical stimulant can be applied on microcapsule to tune the controlled release of active ingredient.

Chitosan coated microcapsules are used for the protection of active ingredients from external factors such as temperature and pH variations. Different types of core materials such as active pharmaceutical ingredients, food products, catalysts, oils and pigments can be microencapsulated using chitosan as shell material [3]. Chemically, chitosan contains free amine groups either in neutral or basic media whereas protonated amines are formed in acidic media. This pH sensitive feature makes the chitosan based compounds suitable in controlled release technologies [4]. Chitosan microcapsules containing drugs as an active ingredient allow their slow release under specific conditions at the targeted sites in the body. For example, lipophilic drugs were encapsulated in chitosan to be effectively released latterly in the intestinal tract of the human body [5]. Similarly, chitosan microencapsulation of vaccines allows their delivery and controlled release on the targeted sites. Fish, neem seed and other essential oils had also been microencapsulated in chitosan to limit their rate of oxidation [6]. Chitosan chains can be cross-linked with glutaraldehyde or citric acid for astaxanthin microencapsulation to increase its antioxidant potential [7]. Chitosan encapsulation of quercetin flavonoids has also been reported to allow their control release targeted as an inflammation therapy [8].

The applications of chitosan microencapsulation are widespread in biomedical, cosmetics, agriculture, food and textile. In this review, we have discussed chitosan chemistry and recent advances made in the previous few years in chitosan microencapsulation process, and various conditions and parameters used for the selection of core and shell materials which effect the encapsulation process.

We have presented current researches concerned with encapsulating various active ingredients in chitosan polymer and its derivatives and discussed the role of chitosan in enhancing the functional properties of active ingredient. Several examples of chitosan microencapsulation of various active ingredients with different chemical nature have been analysed which demonstrate the wider scope of chitosan for microencapsulation for various applications like biomedical, tissue engineering, pharmaceutical, food industry, textile, agriculture and the environment. In addition, this review also provides an insight in to recent advancement in encapsulation techniques based on their advantages and disadvantages.

1.1 Chitosan formation

Chitosan is a linear polysaccharide of [(1→4)-β-linked 2-amino-2-deoxy-d-glucose] that is slightly hydrophilic in nature. Crabs, shrimps and some other crustaceans' shells contain chitin (β-(1→4)-*N*-acetyl-d-glucosamine) which upon reacting with alkaline sodium hydroxide give an *N*-deacetylation product, known as chitosan [9]. The process of deacetylation of chitin to produce chitosan is presented in Fig. 1.

Please insert Fig. 1 here…

Some basic properties of chitosan have been listed in Table 1 which must be considered while working for various applications. Chitosan has been considered a versatile biopolymer that can be amended using various approaches to improve its physiochemical properties thus making it suitable for several desirable applications. Some of biological properties of chitosan along with its applications have been summarized in Table 2, which represents its wide scope of potential applications in various fields. Furthermore, chitosan has also proven itself an excellent biopolymer shell material for the encapsulation of several active ingredients which have been presented in the following text.

Please insert Table 1 here…

Please insert Table 2 here…

2 Microencapsulation

Generally, microencapsulation involves the formation of minute capsules which entrap some active ingredient under some specific conditions and releasing them under other suitable conditions. The encapsulation of active ingredients can be improved by rendering liquids into powders and preventing their clumping which results in protecting active ingredients from oxidation, heat, acidity, alkalinity, moisture or evaporation. It also prevents them from reacting with unwanted species which may induce degradation or polymerization in the system. Encapsulation can also be used for masking unpleasant odour; improving handling of ingredients before processing; releasing active material in controlled manners and finally protecting workers from exposure to toxins [10].

The products of microencapsulation are microparticles, microcapsules and microspheres as shown in Fig. 2. They can be differentiated based on their morphology and internal structure. Microcapsules contain active ingredients surrounded by shells while the microspheres are the matrixes containing active ingredients dispersed inside them. Microparticles vary their size in range from 100 to 1000 nm. Capsules with 1 to 1000 μm diameter are termed as microcapsules [11]. A microcapsule is comprised of two parts; a core and a shell.
The individual particles droplets or liquid materials are typical examples of cores whereas the surrounding coat prepared from different polymeric materials are typical examples of shells. Further, shell materials include polymers, fats, waxes and carbohydrates. Their selection mainly depends on the nature of the core material and the applications of the microcapsule. Microencapsulation is, therefore, a way to protect the core material from temperature, moisture and microorganisms which may otherwise cause harmful effects to the active ingredients inside them [12]. Different approaches are used for microencapsulation as shown in Table 3.

Please insert Fig. 2 here…

Please insert Table 3 here…

The selection of a suitable microencapsulation approach depends on the nature and physico-chemical properties of the encapsulated material. The core material of microcapsule may be an adsorbent particle, suspension of solid or an emulsion [13]. It should be inaccessible to the

surrounding media from unwanted chemical to prevent its deterioration [14]. The encapsulating agents are very important for the microcapsules' stability and efficiency. The criterion for the selection of the encapsulating material depends upon its properties such as compatibility of the shell materials, the structure of the encapsulating agents and the economic and processing aspects involved. One type of a microencapsulating agent may not have all the required properties; therefore, combinations of different microencapsulating agents can be adopted for better production of microcapsules. The choice of an encapsulating agent also depends on the toxicity level, stability, efficiency, protection degree and microscopic properties of the produced micro-particles [12].

2.1 Controlling the morphology of microcapsules

There are three different morphologies of microcapsules which include mononuclear, polynuclear and matrix encapsulation as shown in Fig. 2. The mononuclear microcapsules comprise of shell material surrounding the core material whereas the polynuclear microcapsules contain a shell material surrounding several cores. The matrix encapsulation involves the fine dispersion of core material into the shell material. The basic structures for microcapsule may also contain mononuclear core with multiple shells or microcapsules clusters [15]. The morphology of microcapsules depends on the nature and composition of both core and shell materials and their mode of interaction. The morphology of microcapsules is typically controlled by existing conditions such as temperature, pH and the method used in their preparation.

2.2 The selection of core and shell materials

Core material can either be a liquid or solid coated with polymers, waxes, polysaccharides or proteins depending on the requirement of the produced microcapsule. The dispersed or dissolved materials are typically included in liquid cores whereas active constituents, stabilizers, diluents, excipients and release retardants or accelerators are included in the solid core. The varying composition of the core material provides flexible characteristics to develop the desired properties in a microcapsule. The specific coating/shell on the surface of core material provide suitable physical and chemical properties to the microcapsules. This coating material on the surface of core material should be chemically non-reactive so as not to alter the chemical composition of the core material. The desired properties are achieved in the coating material such as flexibility, impermeability, strength, stability and optical properties etc. [16].

The selection of coating material is a very important step in the encapsulation process because it may have decisive effect on the functional properties of the final encapsulated product. To ensure true encapsulation, the stability of microcapsules, prolong storage abilities, suitable drug release mechanism and resistance against the harsh environment , the following factors should be considered in the selection of core and shell material [17]:

- Solubility of core material,
- Physical state of the core material (either liquid or solid),
- Core reactivity with solvent and wall material,
- Desired size of microcapsule,
- Method for attachment of core to the shell material,
- Release properties of the core material from the microcapsule, and
- The economics of the process and product.

For instance, Ying and co-workers [18] reported the development of chitosan spherical particles in which poly (*n*-butyl acrylate) was encapsulated as an active ingredient. The pad-dry-cure method was used to apply the microcapsules on cotton fabric. Antibacterial activities of the microcapsules were reported to be excellent with up to 99% reduction of bacterial growth. Folate conjugated pluronic chitosan was studied for drug delivery of doxorubicin to cancerous cells. The pluronic micelle containing doxorubicin acted as a core material while the folate conjugated chitosan was used as shell material through some electrostatic interactions. The encapsulated material was effective in the treatment of tumour cells, mainly breast cancer cells in which folate receptors were successfully expressed [19].

2.3 Microencapsulation process and release profile

Microencapsulation approaches can be categorized into chemical, physical and mechanical techniques. Chemical microencapsulation is a versatile method for the encapsulation of drugs. It is further subdivided into complex coacervation, interfacial polymerization and *in situ* polymerization. The coacervation is a phase separation technique with two liquid phases. One phase is called as coacervation phase usually containing polymers while other do not have polymer. The process completes in three steps; in the first step, a polymer of oppositely charged precipitate and process is called complex coacervation. In second step, coacervate is deposited on the dispersed phase, containing active ingredients, and in the third step, the polymer film gets

hardened [10]. In the interfacial polymerization, a reactive polymer is dissolved in two immiscible liquids and the polymerization take place at the interface [20]; while in the *in situ* polymerization, solution of shell material is added into the core phase and the deposition of polymer of core material takes place by changes in the pH or temperate [21]. Some advantages and disadvantages of these techniques have been compared in Table 3.

The microencapsulation process is generally divided into three major stages. In the first stage, some active constituents are incorporated into the matrix or the core of microcapsules which may be in the form of emulsions or suspensions. In the second stage, the liquid form of the matrix makes a dispersion and the solid matrix through spraying a solution under agitation. In the last stage, droplets are stabilized by different physicochemical approaches. The releasing mechanism of the core material depends upon the nature of stimulant and the morphology of microcapsules. The microencapsulation ensures the stabilization and immobilization of the active constituents whereas the coating permits different levels of release and protection [22]. A schematic process of a drug microencapsulation and its release profile have been shown in Fig. 3.

Please insert Fig. 3 here…

2.4 The conditions for microcapsules formation

Many parameters or conditions should be considered while preparing microcapsules as their yield is greatly influenced by temperature and pH conditions. The following features may be considered to achieve efficient production of microcapsules [23]:

- Size of particles, morphology of microcapsule, encapsulation efficiency and drug release rate may be affected by the ratio of active ingredient to encapsulating material.
- For chitosan microcapsules preparation and agitation speed considerably affects the cross-linking reaction and emulsification process. The agitation method and speed are affected by the intrinsic viscosity of chitosan aqueous solutions. Microcapsules yield may be maximum at higher agitation speeds ensuring proper homogenizing [24].
- The yield of microcapsules depends on the concentration of shell materials. The releasing behaviours of the core content depends on the ratio of core and shell materials. The concentration of shell material is directly related to microcapsule yield.

- The microcapsule shell strength and surface adhesion properties are influenced by cross-linking time and the yield. In short time, chitosan polymer may not completely cross-linked with the linking agent producing low yield [25].

Various studies have been conducted to investigate the effect of the above-mentioned parameter on chitosan encapsulation efficiency. For instance, some researchers [26] had encapsulated cortex moutan (a drug for hypertension treatment) in chitosan and investigated the effect of chitosan concentration on its encapsulating efficiency, it was observed that when the chitosan concentration was increased from 2 to 6% (w/v) its encapsulating efficiency increased significantly. They concluded that when the concentration of shell material increased the diffusion of drug decrease, accordingly. While studying the effect of ratio of active ingredient to encapsulating material, Devi and co-workers [27] observed that when ratio of core to shell material decreased form 1/50 to 1/300, the encapsulation efficient increased significantly. Kapadnis and co-workers [28] investigated the effect of degree of deacetylation of chitosan on the encapsulation of bovine serum albumin (BSA). They observed that BSA was efficiently encapsulated at high degree of deacetylation due to a higher number of functional groups on chitosan which increased its encapsulation efficiency. Han and co-workers [29] studied the effect of agitation speed (500, 800 and 1100 rpm) on the yield percentage of microcapsule. They observed maximum yield of 1100 rpm, when cortex moutan was homogenously mixed in chitosan solution for efficient encapsulation.

2.5 Specific examples of chitosan microencapsulation

Chitosan is the second most abundant natural biopolymer after cellulose and it has several amino and hydroxyl functional groups [30]. Due to the presence of positive charge on its amino groups, chitosan is the only commercially available water-soluble cationic polymer so far [31]. Furthermore, chitosan is pH sensitive due to the presence of D-glucosamine in its structure. These unique properties make chitosan an important shell material to entrap various active ingredients suitable for several applications in different fields. Many drugs can be encapsulated for targeted delivery approaches. Active food ingredients can also be encapsulated to protect them from microbial attack and to enhance their nutritional value. Chitosan can also be used to encapsulate vitamins for their applications in foods, cosmetotextiles and pharmaceutical industry. Chitosan encapsulation of essential oils, lipids, hemoglobin, astaxanthin and quercetin has found

diverse applications [32, 33]. Some specific examples of chitosan encapsulation of various active ingredients are illustrated below.

2.6 Chitosan encapsulation of essential oils

Essential oils can be used as antimicrobial agents however they are not widely used due to their volatility. Chitosan encapsulation is important for the slow release of essential oil ensuring the increased duration of oil availability to the required target [34]. Some researchers suggested that the essential oil of pimento was encapsulated into chitosan microspheres and chitosan/k-carrageenan microspheres, separately [35]. The pad-dry-cure method was used to incorporate fabricated microcapsule on the cotton fabric using dihydroxy ethylene urea as a cross linker. Essential oils were encapsulated into chitosan microsphere (as shown in Fig. 4) to investigate their releasing property with chitosan/k-carrageenan microspheres. Chitosan microcapsule showed an effective release of the essential oil to control fungal and bacterial growth in comparison to chitosan/k-carrageenan microspheres [36]. Therein, FTIR and SEM confirmed the cross-linking within microcapsules. The concentration of chitosan and essential oil had determined the extent of antibacterial activity. The stiffness increased at higher concentration of chitosan and was decreased on increasing the essential oil concentration [37].

Please insert Fig. 4 here…

2.7 Chitosan encapsulation of neem seed oil

Neem seed oil (NSO) extract is effectively used to control insects and pests on plants however due to their garlic or sulphur like odour, its use is limited in cosmetics and medicine products. The microspheres of NSO in a polyelectrolyte complex of chitosan and carrageenan had been prepared using complex coacervation as shown in Fig 5. The surface of the microcapsules became irregular as more oil was encapsulated inside them [6]. The burst release of NSO became more gradual on increasing the polymer concentration, the percentage of oil and the concentration of glutaraldehyde as crosslinking agent. The DSC analysis showed an absence of any interrelation and poor compatibility between the polyelectrolyte complex of chitosan and the carrageenan [38]. Chitosan and κ carrageenan were used to encapsulate NSO using three different cross-linkers (i.e., genipin, glutaraldehyde and tannic acid) to compare their effect on the release behaviour of the microcapsules. Therein, glutaraldehyde was found to be the best cross- linker to improve thermal stability, release behaviour and water uptake capacity of

chitosan microcapsules [39]. Both FTIR and the DSC analyses confirmed the absence of chemical interaction in microcapsules, but the release of NSO was entirely dependent on the cross-linker. The more the cross-linking agent used the less release of NSO occurred. I has therefore been concluded that microencapsulation of NSO can effectively be used as pesticides, insecticide and herbicide [40].

Please insert Fig. 5 here…

2.8 Chitosan encapsulation of emulsified lipids

Long-chain polyunsaturated omega-3 fatty acids, especially eicosapentaenoic acid (EPA, C20:5 ω3) and docosahexaenoic acid (DHA, C22:6 ω3), are important to prevent cardiovascular disease, rheumatoid arthritis, diabetes, allergies and Alzheimer's diseases [44]. The ability to microencapsulation of fish oils is therefore important to increase the nutritional value for such necessary food products. The stability and shelf life of fish oil and other bioactive and food components was improved by chitosan encapsulation preventing their auto-oxidation as compared to bulk storage. Such encapsulation had no significant effect on its *in-vivo* digestibility [41-43]. Therefore, some long-chain polyunsaturated omega-3 fatty acids isolated from fish oil were microencapsulated into chitosan shell using spray drying technique to reduce their susceptibility to ambient oxidation. The results showed enhanced stability and storage duration for these fish oil extract [44]. In a study, chitosan encapsulation of fish oil was also done using an ultrasonic atomizer through an emulsification method. As a result chitosan was not only capable to give a stable emulsion but its stability was enhanced with mediated with maltodextrin [45]. Likewise, milk originated shell materials had also been used to encapsulate fish oils using spray drying technique resulting in an increased encapsulation efficiency by increasing the temperature of inlet used for drying air to reduce moisture contents [46].

2.9 Chitosan for α-lipoic acid encapsulation

Chitosan had also been accepted as an effective method for α-lipoic acid (ALA) encapsulation. It prevents decomposition of ALA at elevated temperatures and provides an efficient delivery process. ALA was encapsulated in dry chitosan microbeads by swelling them in its respective solution. FTIR and differential scanning calorimetry (DSC) analyses revealed interaction of hydroxyl/amino groups of chitosan with the carboxylic acid groups of ALA. Its encapsulation efficiency was observed in the range from 46.8 to 58.5%. The retention of the non-extractable

ALA in the chitosan medium could deliver a continuous release of this antioxidant for a long period [47]. Liposomes containing coenzyme Q10 and ALA coated by chitosan were efficiently compared with uncoated liposomes. Hydrogen bonding and ionic interactions in chitosan-coated liposomes with ALA were enhanced showing effective radical scavenging capacity and sustained drug release behaviour [48]. The ALA-chitosan complex was formed showing ALA release due to changes in pH values. The ALA is used for energy production in the mitochondria acting as a cofactor. Its stability had been improved by chitosan encapsulation for safe release in the gastrointestinal tract [49]. The ALA had also been encapsulated in poly (ethylene oxide)/chitosan using single-capillary electrospray system. Excellent dispersity and stability of particles in suspension was observed under DLS based zeta potential measurements. The results demonstrated effective anti-inflammatory activity for poly(ethylene oxide)-chitosan coated ALA in comparison to free ALA solutions [50].

2.10 Chitosan encapsulation of drugs

The efficiency of various pharmaceutical products could be improved by encapsulating the drugs into suitable shell materials. This does not only protect them from harsh external environment but also provide them with more effective properties and improve their bioactive roles in the human body. Controlled drugs release rate could be obtained from chitosan coated microspheres which might be suitable for oil soluble drugs. Among others approaches, gelation and emulsification techniques had been considered excellent for intestinal delivery of lipophilic drugs due to improve their encapsulation efficiency [5].

A microfluidic approach had been used to prepare double emulsion precursor for burst release of a hydrophobic drug coated with chitosan in acidic medium [51]. Chitosan is soluble in acid media while in neutral and basic media, chitosan microcapsules remain insoluble and maintain their morphologies. Thus, the microcapsules could decompose its shell in acidic media releasing their active ingredients making them suitable to target areas such as the stomach at pH<4. Any pH fluctuations greatly influence the properties of chitosan microcapsules [52]. Likewise, metronidazole is an antibiotic which is used to treat bacterial infection on skin, stomach and joints and is also used to treat inflammatory bowel disease [53]. It had been encapsulated in alginate beads mediated with different chitosan concentrations to develop some mucoadhesive properties. The encapsulation efficiency, surface morphology, swelling behaviour, and *in vitro*

and *in vivo* drug release profiles were assessed. Subsequently, it was observed that chitosan with high concentration showed efficient encapsulation and controlled drug release rate at pH 7.4 with extend exposure period [54].

Tissue engineering helps improve the functions lost due to some pathological condition and damaged or diseased tissues [55]. Chitosan is an important material for tissue engineering and wound dressing application due to its biocompatibility [56]. Karpuraranjith and co-workers [57] had synthesized chitosan-*g*-β-cyclodextrin (chit-*g*- β-CD) scaffolds using freeze drying approach as active filling material during the treatment of damaged tissues. The β-CD made it efficient for drug loading as it improved the swelling behaviour of chitosan by decreasing its degree of hydrogen bonding. Ketoprofen is a nonsteroidal anti-inflammatory drug which was encapsulated in chit-*g*-β-CD and its loading efficiency was observed to be increased at high concentration of chit-*g*-β-CD because β-CD increases the hydrophobic interaction with the ketoprofen molecules. The kinetic study showed that at initial stage, the drug release rate was high due to the presence of possible uncoated drug at the surface of shell. The drug release rate become slow and equilibrium was observed after 23 h. The slow release of the drug was due to complex formation between drug and the chit-*g*-β-CD. The nontoxic behaviour made it efficient for cross-linking of glutaraldehyde against the fibroblasts (L929) cells and the chit-*g*-β-CD; therefore, has become an important scaffold for tissue engineering applications.

Chitosan is also used for non-viral gene delivery. Chitosan contains slightly positive charge in acidic media which allows the attachment of nucleic acids to the cationic chitosan. The DNA, siRNA and nanoparticles of nucleic acid could therefore be attached to chitosan for genes delivery [58]. However, its poor solubility in water makes it less efficient when compared with other synthetic cationic polymer such as polyethylenimine (PEI) and poly-L-lysine (PLL) [59]. Chitosan based nanoparticles could also be used for diagnostic purposes [60]. In a study, glycol chitosan (GC)-based nanoparticles were used to entrap the siRNA and chemotherapeutic drugs [61]. The encapsulation of doxorubicin (DOX) into chitosan formed DOX-CNPs whereas Bcl-2 si-RNA formed some si-RNACNPs. The encapsulation of drugs with CNP gave similar *in vivo* distribution and chemical kinetics [62]. Some researchers suggested that chitosan encapsulated poly(lactic-co-glycolic acid NPs could be used for magnetic resonance (MR) imaging of cancer cells [63]. These nanoparticles were also encapsulated with paclitaxel for the treatment of cancer. Glycol CNPs interaction with 5β-cholanic acid was based on chemical modification to confirm

nano-carriers for drugs encapsulation which was efficient for tumour targeting. It was concluded that tumour-targeting ability was long lasting through the angiogenic vessels of tumour tissues.

2.11 Chitosan for haemoglobin encapsulation

Haemoglobin is an important constituent of blood carrying oxygen towards cells and tissues. For oral bioavailability of haemoglobin, encapsulation approach has been more efficient and protect it from desaturating at high temperatures and in organic solvents. The proposed process of haemoglobin encapsulation in chitosan is shown in Fig. 6. The microencapsulation was investigated to determine if it may increase the oxygen carrying capacity and the *in vitro* releasing behaviour of haemoglobin [64]. Therein, freeze-dried bovine haemoglobin was encapsulated using chitosan or calcium alginate beads. The procedure was optimized for the formation of beads containing more than 90% of initial haemoglobin contents. The haemoglobin dissociates into its monomer and was released at pH 1.2 due to loss of interaction between negatively charged alginate and positively charged haemoglobin that exists at pH 5.5. Globular proteins and cells could be encapsulated using this method [65].

In another study alginate beads containing microencapsulated haemoglobin were coated with a dextran derivative for comparison between dextran and the chitosan. On changing the media pH from 3 to 4, the bonding interaction between beads and haemoglobin weakened ultimately releasing the haemoglobin. Dextran allowed slower haemoglobin release in comparison to chitosan [66]. The *in vitro* releasing behaviour of haemoglobin was evaluated using chitosan coating in three different conditions, namely uncoated, incomplete and completely coated microspheres. In the gastrointestinal tract, haemoglobin was quickly released from the uncoated and incomplete coated microspheres at pH 6.8 while the complete coating gave a slower release even at pH 1.2 [67]. The encapsulated haemoglobin affinity for oxygen binding was generally similar to that of the purified haemoglobin [64].

Please insert Fig. 6 here…

2.12 Chitosan encapsulation of astaxanthin

Astaxanthin is a ketocarotenoid belonging to the terpenes class with antioxidant potential of 100 times greater than the β-tocopherol to protect skin against cancer and is used as anti-inflammatory and immunostimulants agent [68]. It has been suggested that astaxanthin could be

encapsulated in chitosan to enhance its stability and to evaluate its isomerization at different temperatures [69]. A solvent evaporation method was used for the microencapsulation of astaxanthin in the chitosan using glutaraldehyde as a cross-linker. Microcapsules in powdered form were obtained with diameter in the range of 5-50 μm. The stability of these microcapsules was investigated under different storage conditions at temperatures 25, 35 and 45^{o}C for 8 weeks. When the astaxanthin pigments were extracted from the chitosan microcapsules using a solvent mixture of methanol/dichloromethane to evaluate it using HPLC, it was observed that the microencapsulated astaxanthin was neither degraded nor isomerized. Kittikaiwan et al. [70] reported that *Haematococcus pluvialis* was used as a natural source of astaxanthin and was encapsulated in porous chitosan films (of 100 μm thickness) to evaluate its antioxidant activity. The chitosan coating prolonged the storage of astaxanthin with only 3% loss of antioxidant activity protecting against oxidative environment.

2.13 Chitosan encapsulation of quercetin

Quercetin is also an antioxidant, anti-inflammatory and anti-tumour agent found in apples, grapes and onions [71]. Quercetin was encapsulated to study its controlled release properties for desirable biological activities. Hao et al. [72] reported the use of spray-drying technique to obtain the microcapsules containing the flavonoid of quercetin. Chitosan had been used as suitable functional material for flavonoids microencapsulation to attain better resisting properties against harsh environment with desirable antioxidant activity under effective controlled release. Theoretically, flavonoids could efficiently entrap reactive oxygen species (ROS) due to their antioxidant potential [73].

Chitosan and xanthan gum were used within microencapsulated quercetin to ensure its controlled release in the colon for inflammation therapy [74]. Similarly, chitosan coated nano-liposomes containing quercetin proved its effectiveness in controlled release of quercetin giving enhanced stability and anti-proliferative activity and is therefore being considered as novel nanocapsules for the delivery of hydrophobic chemicals and storage of food products. The kinetic study showed that quercetin release delayed from the chitosan-based film when irradiated with an electron beam of 2.2 MeV energy. Such irradiation produced free radicals which helped cross-linking between chitosan film and the quercetin which increased the stability of encapsulated

quercetin due to more linkage with the chitosan. This also prevented the burst release of core material from the biopolymeric matrix [75].

2.14 Chitosan encapsulation of vaccines

Vaccines are important to protect body against pathogens and infectious diseases and their encapsulation is important to increase their immunogenicity. Jiao et al. [76] reported that a coacervation method was used to encapsulate diphtheria, tetanus toxoids and whole cell *pertussis* (DwPT) antigen using chitosan as shell material. Therein, vanillin was used as a cross-linker while sodium tripolyphosphate (STPP) as co-cross-linkers to develop the encapsulated vaccine. The encapsulated antigen in the chitosan microspheres exhibited mucoadhesive properties and controlled release of proteins which was suitable for oral vaccine development of the trivalent DwPT. For porcine nasal mucosa, chitosan coated poly(D,L lactic-co-glycolic acid) (PLGA) was investigated to compare its properties with $Al(OH)_3$ coated PLGA. They observed that the tissue adhesion properties increased with the chitosan encapsulated PLGA via trans-cellular path acting as nasal vaccine carrier while $Al(OH)_3$ encapsulated PLGA proved to be effective for tissue uptake, permeation and the adhesion for nasal mucosa cells. There also observed increased immunization using chitosan derivatives acting as a vaccine carrier [77]. The microspheres containing mannose had been used for improved DNA delivery into antigenic cells. Intramuscular injection was also used to deliver the vaccine in mice. The controlled release of DNA was observed with increased immunogenicity for chitosan microspheres proving to be a safer vaccination process for mice [78] .

2.15 Chitosan encapsulation of vitamins

The vitamin A, C, E and K are known as liposoluble compounds naturally found in food products. For pharmacological purposes, vitamins can be used to cure skin disease, cancer and the oxidative stress. Microencapsulation of vitamins may protect them from heat, light, oxygen and allows their slow release in order to prevent hypervitaminosis [79, 80]. Some details of selected vitamins encapsulation processes and subsequent effects are presented below.

2.15.1 Chitosan encapsulation of vitamin C

Vitamin C (ascorbic acid) is a water-soluble compound found in various foods and its deficiency causes scurvy and has diverse applications in the fields of biology, pharmacology and

dermatology. It helps strengthen the immune system and minimizes the risk of some severe diseases such as cancer, heart diseases and high lead (Pb) levels [78] . The human body can't synthesize vitamin C or store it, therefore it must be taken through dietary nutrients, regularly. The sources of vitamin C include citrus fruits and green vegetables [81]. Vitamin C sensitivity towards pH, temperature and heat cause its spoilage in food therefore microencapsulation may help protect it from oxidative environments [78]. Spray drying technique has been used for encapsulating vitamin C (as shown in Fig. 7) because it causes minimum loss of ascorbic acid, both thermal phase separation and melt dispersion are effective for its release [82]. STPP was used as cross linker for encapsulation of vitamin C in double layered chitosan structure which proved effective for its controlled release in the gastric secretions and the intestinal fluids. It was observed that the encapsulation efficiency decreased on increasing the concentration of the crosslinking agent; this may be due to surface irregularities of chitosan. For control release and better encapsulating efficiency an appropriate amount of crosslinking agent should always be used [83] .

Please insert Fig 7 here….

2.15.2 Chitosan encapsulation of Vitamin D

Vitamin D exists in two main chemical forms; the first form is known as vitamin D_3 or cholecalciferol while the second form is D_2 ergocholecalciferol. The skin of the human body is able to synthesize vitamin D_3 upon exposure to sunlight. Calciol, calcidiol and calcitriol are different forms of vitamin D_3 which is important for bone metabolism, blood pressure, immunity, insulin secretion and homeostasis [84]. The second form D_2 is present in food matrixes and can be released to form mixed micelles because it is lipophilic in nature. It enters in enterocytes, chylomicrons and the liver where it is activated for use as deficiency causes rickets, osteomalacia, fatigue and depression [85]. Carboxymethyl chitosan (CMCS) and soy protein isolate (SPI) complex nanoparticles had been studied to check the effect of Ca^{2+} concentration, pH and CMCS/SPI mass ratio. Vitamin D_3 was encapsulated into CMCS/SPI polymeric complex. Lower concentration of Ca^{2+} was required for CMCS/SPI complex in comparison with CMCS for broad range of pH values. The encapsulation efficiency of the complex nanoparticles was high due to its compact structure. Vitamin D_3 release was observed to be significantly higher under simulated intestinal conditions in comparison with gastric fluids. The use CMCS/SPI

complex nanoparticles were reported to be suitable for both encapsulation and controlled release of bioactive and hydrophobic nutraceuticals [86] .

Khan et al. [87] reported that chitosan was used to coat the zein nanoparticles for encapsulation of vitamin D3. Uniform and true encapsulation was obtained on adding calcium source. The encapsulation efficiency obtained after coating with the addition of nanoparticles was 87.9%. Rabelo et al. [88] reported on a nanostructured lipid carriers (NLCs) coated with chitosan for encapsulation of vitamin D. The selection of lipid was based on higher encapsulation efficiency. Stearic acid (SA) and oleic acids (OA) were used in 70:30 (v/v) for the encapsulation of vitamin D due to their compatibility, stability and higher encapsulation efficiency. Chitosan coated NLCs showed excellent stability and storage without expulsion of vitamin D. It was concluded that a physically stable system was obtained after encapsulation of vitamin D. Tan et al. [84] reported using chitosan to entrap vitamin D_2 with ethyl cellulose coating via spray drying technique and was mainly used for controlled release of vitamin in intestinal juice for effective absorption.

2.15.3 Chitosan microencapsulation of vitamin E

Alpha tocopherol (vitamin E) is an environmental friendly dark viscous yellowish-brown oily substance with exceptional thermal stability and limited volatility [89]. Alpha tocopherol is important for food packaging to keep items afresh. It is present in different foods to protect lipids from auto oxidation and thus, increasing their shelf life. Its nature is hydrophobic and gives intense response in heat, oxygen and light. Its hydrophobicity minimize its applications in different fields of life [90]. It plays important role in the protection of skin from harmful UV-light through absorption while giving antioxidant defence to the skin [91]. Both retinoic acid and alpha tocopherol are highly effective for dry skin but has limitations for use in cosmetics due to their sensitivity towards light and oxygen and some adverse reactions in localized areas such as erythema, xerosis and mild scaling. These problems could be controlled by their microencapsulation in chitosan shells, which protects from heat and light exposure. For topical applications, skin irritation can be minimized by incorporating retinoic acid and alpha tocopherol in chitosan microspheres. The stability and release time cam be increased for chitosan containing vitamins giving thermodynamically favourable applications [92] .

The microencapsulation also protects the alpha tocopherol as a core material to regulate the delivery process [93]. The presence of polyunsaturated fatty acids in the biological membrane

makes them susceptible to oxidation by free radicals. Alpha tocopherol protects the membrane by converting the free radicals into stable species through their hydrogen bonding. The esterification process also gives stability to alpha-tocopherol but this molecule is at a risk of long term degradation [94]. Kaleem et al. [95] reported that the antioxidant activity of alpha-tocopherol was dependent on their capability to give their alcoholic hydrogen to lipids.

3. Chitosan based microcapsules applications

Chitosan had found vast applications in the biomedical, textile, cosmetics, food and agriculture related industries. Chitosan is beneficial for wound dressing, gene delivery and tissue engineering, and treatment of acne, dermatitis and hair problems [96]. Chitosan have been used in encapsulating various food materials such as flavours, essential oils, vitamins, enzymes and aroma to protect them from degradation and control their release [97]. Chitosan has different environmental applications like remediation of inorganic and organic pollutants having toxic metals and dyes, traces of contaminants in soil and water bodies [98]. In recent days, chitosan has emerged as excellent biopolymer having potential applications in various fields such as drug functional additives, pharmaceuticals, agriculture and cosmetics [99].

Chitosan encapsulation may also improve the properties of encapsulated cosmetics and also provide protection from external adverse environment. Human skin glands excrete sebum which reacts with amino acids and the lactic acid of sweat to make skin surface mildly acidic at pH 5.5. The pH of most cosmetics has a range 5.5 to 7; therefore, these cosmetics must be encapsulated to allow the controlled release of different active agents. In drug delivery, chitosan is used as a coating material giving many advantages such as bio-adhesive properties, improvement and sustained drug release [100]. In a study investigating diclofenac release, 50% occurred within one hour when using uncoated microspheres while only 14.6% with the chitosan coated microparticles [101]. An exciting application of chitosan had been reported with calcium phosphate as a cementing agent where chitosan glycerophosphate combines with calcium phosphate and citric acid to form a self-hardening system for bone filling and repairing [102] .

Chitosan membranes offer excellent permeability and high tensile strength making it suitable to use as an artificial kidney membrane [103]. The novel semipermeable membrane was established for better control of blood compatibility and transport materials. Patients who suffer from skin problems or severe infections and fluid loss, can be treated using chitosan capsule of novel

membrane [104]. These early symptoms require the rehabilitation and replacement of these skin problems by using chitosan membrane which acts as a biodegradable template for the synthesis of neodermal tissues. Chitosan polymer also has structural features that are similar to glycosamine glycans which can be considered for the development of substratum for skin replacement [104]. Chitosan microcapsules have great significance for the chromatographic supports. These spheres interact with the organic substances like lipids and proteins acting as electron donors for different metal ions [105].

Recently, chitosan has been used for the coagulation of suspended solid particles. According to the USA Environmental Protection Agency, chitosan is readily accepted for water applications [106]. The presence of chitosan in various fungi indicates that chitosan is already a part of human food. Different studies showed that chitosan is as safe as sugar and salt and can act as an active agent for food processing and biological activities such as hypocholersterolemic and hypolipidemic activities [107].

3.1 Specific applications in textiles

Chitosan fibres are well known bio-functional fibres but other chitosan-based material such as bioyarns, biothreads and fragrant biofibres are not well known compared to chitosan fibres. Studies demonstrate that novel fragrant biofibre and yarn were prepared by Schiff base using fragrant aldehydes such as n-decylaldehyde [108]. A small portion of aldehyde was slowly released from the fibre and yarn in open air and a little amount was released in the dry close vessels [109]. Essential oils were microencapsulated into chitosan for different purposes for example citronella essential oil is volatile and when encapsulated into chitosan can be used as mosquito repellent on textile surface [110]. Other essential oils as linseed oil, lemon and oil phase change materials were also encapsulated into chitosan for their applications in the textile industry [111]. Chitosan encapsulation was also use for fragrance finishing on fabrics as it reduced their evaporation rate and increases their staying duration. Chitosan encapsulated rose fragrance forming nanoparticles by ionic gelification was applied on cotton fabrics [112].

Alpha (α)-tocopherol is an excellent antioxidant but under oxidizing conditions it show less stability which limit its applications. Raza and co-workers [113] encapsulated the alpha (α)-tocopherol in chitosan nanospheres which enhanced its stability in oxidative environment and prolonged its control release. Chitosan encapsulated α-tocopherol application on cotton fabric

was investigated and it was observed that it causes little decrease in tensile strength while on the other hand increased its antibacterial efficiency.

In another study, we also synthesized silver nanoparticles (SNPs) using chitosan polymer as stabilizing as well as reducing agent and applied on viscose fabric surface by in situ treatment [114]. Investigating the textile properties of viscose fabric, we observed that chitosan- SNPs treated fabrics showed excellent antibacterial properties while maintaining fair textile properties. In another study the authors investigated chitosan encapsulated poly(lactic acid) nanosphere and its antibacterial activity by applying it on hydrophobic textile fabric like polyester and subsequently on woven polyester fabric though a cross linker. Its imparted good antibacterial properties to the fabric [115].

Zhu et al. [116] reported that complex coacervation methods were used to produce microcapsule containing limonene and vanillin as core material while using chitosan and Arabic gum as shell material. Tannic acid gives hardening effects to microcapsule. Sustained release pattern of active agent was obtained from the microcapsule for 7 d at 37°C. Microcapsules were grafted onto cotton fabrics using esterification reaction between microcapsule and the citric acid which are followed by thermo-fixation and curing using citric acid as a nontoxic cross linker. These microcapsules showed effective action against bacteria after incorporation onto fabrics. Fabrication of active agent allows its loading for finishing purpose or using on textile surface for dressing purpose in the form of films that are mainly useful for wounds healing and the treatment of skin diseases including skin injuries [117] .

Son et al. [118] reported that pad dry cure method was used for fixing vitamin E microcapsule on dyed cotton knit. Natural indigo was used as dying agent for cotton knit and treated with microcapsules containing vitamin E including softener agent. SEM analysis confirmed the microcapsules fixation on cotton fibres. Vitamin E concentration gradually decreased with time as confirmed by LC-MS. Softness improved due to the softener, but air permeability decreased. This was a reliable method for durability and colour stability for the treated fabrics. Turkoğlu et al. [119] reported that complex coacervation technique were used to prepare microcapsule containing vitamin E which was implemented on cotton fabric using the padding method. The capsule average diameter was 280nm. The small size alpha tocopherol made its incorporation into fibre gaps easier. Most of the capsules were found attached to fabrics even after several

washings. Sequential studies carried out on fabric containing alpha tocopherol showed that it remained attach to the fibre gaps providing considerable antioxidant activity which was essential for the maintenance of the fabric integrity.

3.2 Applications in paper industry

Chitosan has a great potential for pulp and paper industry. In paper industry, the surface of paper is treated with a 1% solution of chitosan to increase its folding endurance and bursting strength while the brightness of paper is maintained [120]. With the development coloured photocopying, high quality fibres are required for papers. The treatment of fibre with 0.5% solution of chitosan improved colour fastness of fibre. In the area of paper making industry, a chitosan layer is placed on photographic paper because of increased antistatic characteristics and increased electrostatic discharge which leads to a decrease in picture quality. The surface resistance due to these charges were increased more than 10,000 times after the treatment with chitosan solution [121].

3.3Applications in agriculture

Microencapsulation can achieve controlled release of active agents in pesticides, herbicides and insecticides [122]. In organic agriculture, microencapsulated materials are released on to plant for growth stimulation and controlled release of specific chemicals using anionic clay nanocomposites. Food products based on nanomaterials are prevented by organic food certifiers [123] . Nano-imidacloprid encapsulated material was used for controlling pests of vegetables in the field. Chitosan and alginate were used for encapsulation of SDS (sodium dodecyl sulfate) modified Ag/TiO2 imidacloprid nano-formulation. Testing was carried out on soybeans plants that were planted into soil with 3.1% dry matter content and pH 6.2. The degradation rate was monitored for plants and was faster during the first eight days and minimum after 20 days [124] .

3.4 Applications in food industry

Microencapsulation is usually followed by the incorporation of active food ingredient such as enzymes, cells, or other materials in small capsules. Sensitive food components are protected in microcapsules offering better food processors against nutritional loss. Microencapsulation allows the control release of the active food ingredients at specific sites at the right time giving higher functional features. The effectiveness of food additives is typically increased by the released functional moiety which broadens the application of food ingredients. Microencapsulation turned

reactive, sensitive, or volatile additives (vitamins, cultures, flavors, etc.) into a stable component of food [125]. Active ingredients incorporation into food and dairy products improves their nutritional worth. Calcium in orange juices, omega-3 fatty acids in eggs and guarana in sunflower seeds can be incorporated as active ingredient. Microencapsulation involves the formation of microcapsule containing shell material to entrap functional components as a core material with a few microns diameter capsule. Functional food components are uniformly coated with shell material to effectively separate the internal phase from surrounding material. Phase separation is important for increasing nutritional worth, masking off flavours and extending their storage time without any adverse effects on physical, chemical and functional properties. Microencapsulation is important therefore to increase the stability and storage imparting some important characteristics such as size distribution and morphology, and *in vitro* and *in vivo* release characteristics [126].

3.5 Applications in pharmaceuticals

The studies showed that spherical beads of Indomethacin (anti-inflammatory drug) had been prepared by dispersing drug in chitosan solutions of sodium tripolyphosphate [127] . Spherical beads were prepared with narrow particle size distribution and high drug content allowing easier ability to fill into capsules or compress into tablets. A chitosan microsphere of ketoprofen was prepared by a multiple emulsion method. Oil in water emulsion provided an appropriate method for the fabrication of microparticles with suitable yield [128] . Chitosan derivatives are very useful in various biomedical applications as it has biocompatible properties like cell growth efficiency and blood compatibility. Grafted chitosan materials are beneficial for cardiovascular applications while chitosan membranes permeability with HEMA (2-Hydroxy ethyl methacrylate) can be used in the dialysis machine [129] .

3.6. Biomedical applications

Chitosan is suitable for medical application because of its unique properties described before including the presence of reactive functional groups (-NH_2 and -OH), biocompatibility with the tissues, gel forming ability, high adsorption capacity, anti-bacterial, antithrombogenic, anti-tumor antifungal activities and bioadhesivity [130]. It has therefore been used for the encapsulation of various drugs and their control release [65]. For instance, DNA can be encapsulated into the chitosan nanomaterial by coacervation technique and chitosan at neutral pH

protecting it from degradation by nucleases. When chitosan was crosslinked with pluronic molecules using ultraviolet radiation, a thermo-sensitive hydrogel was formed which have various potential application in medical science [131] such as growth hormones and plasmid DNA encapsulation and controlled release.

Chitosan nanomaterials have also been used for in vivo molecular imaging. It can encapsulate Fe_3O_4 (imaging agent) for magnetic resonance imaging (MRI) and enhancing the hepatocyte targeted imaging [132]. In biomedical application chitosan Nano carrier for Cancer therapy has gained much importance and anti-cancer drugs and their release at the tumour sites has extensively been studies. He et al. [133] investigated using chitosan nanoparticles for encapsulating the anticancer drug, 5- Fluorouracil (5-FU). The chitosan encapsulated 5- FU microcapsule possess the desired laser light absorption ability and polymer hydrolysis at the tumour site effectively destroying the cancer cell using laser light. The efficiency and bioavailable of chitosan encapsulated drugs were much higher when compare with conventional drugs. This is because of chitosan's true drug encapsulation ability and mucoadhisive property which lead to prolong interaction between drugs at the target site. Chitosan encapsulation of analgesic peptides bola-amphiphilic vesicles and its delivery across the blood‑brain barrier and its prolonged analgesic activity was also reported [134]. The summery of biomedical applications of chitosan-based microcapsules is given in Table 4.

Please insert Table 4 here…

3.7 Application in tissue engineering

Tissue engineering has emerged a new concept for the treatment of various diseases and injuries. It involves cell biology and molecular techniques with advanced materials in the regeneration of tissues. The human body has only limited capacity to repair every injured or diseased tissue mainly for skin and bone tissues. Tissue engineering technique interestingly provides some solution by regenerating new tissues replacing the disease tissues [135]. Hydrogel scaffold are used in tissue engineering where cells are encapsulated during the scaffold formation. These scaffolds provide support to cell growth and tissue development. The properties of hydrogen like swelling, mechanical properties, diffusion and degradation are usually suitable for the cell growth and would not affect the entrapped cell during the degradation process at target site. Chitosan has been considered as suitable candidate for cell encapsulation. Its properties are pH

dependent, where at acidic pH it become positively charged and water soluble while it forms solid hydrogel at pH of physiological system, where it exists as neutral and being hydrophobic. The presence of several amino and hydroxyl groups on chitosan facilitate its chemical modification. Water solubility of chitosan at physiological pH can be enhanced by grafting with methacrylic acid. In a previous study chitosan was grafted with polylysine to enhance microenvironment for the neural cell growth [136].

3.8 Environmental applications

Wastewater generation and treatment is an important serious environmental issue particularly those generated by the textile, paper, leather and printing industries which contain significant heavy metal ions and dyes. To, date several techniques like biodegradation, coagulation, ion exchange, membrane filtration and adsorption have been used to eradicate water pollutants. In recent days chitosan-based composites have been used for wastewater treatment. Bagavathy and coworkers [137] encapsulated zinc oxide (ZnO) nanoparticle with Chitosan for dye adsorption from waste water. They investigated the adsorption of dye at different parameters and observed excellent removal efficiency. They also investigated the antibacterial efficiency of encapsulated material against Gram-positive and Gram negative bacterial and observed that chitosan effectively inhibited their proliferation. Global warming is a serious threat to the environment and extensive of petroleum in automobiles and industries making this issue wors [138]. Biofuels like ethanol and biodiesel can be a better alternative as they do not produce toxic gases like sulfer oxides upon burning. Immobilization of lipase by chitosan encapsulation for biodiesel production is gaining much attention because of the ecofriendly nature of biodiesel [139].

3.9 Critical analysis

Due to excellent biocompatibility nontoxicity, antibacterial and mucoadhesive properties chitosan polymer has attracted much interest and developed potential applications in various fields specially drug delivery, tissue engineering, biosensor, would healing, bioimaging, diagnostics, gene therapy, food technology and environmental technology as encapsulating material for active ingredients. Chitosan is a biological compactible and chemically (-OH and -NH_2) versatile coating material. Owing to the superior properties of chitosan polymer over the other polysaccharides it not only increases the shelf life of encapsulated drugs by protecting them from harsh environment but also control their release rate. Chemically chitosan can be modified

using different crosslinking agents as describes earlier which help in control release mechanism of the drug especially anticancer drug doxorubicin release. Most of the drugs fail at clinical phase due to their inability to reach the targeted sites and also due to their negative side effects.

Chitosan mucoadhesive property has provided a promising solution of this issue by targeting drug delivery system in which drugs are released only at the action sites. Chitosan has the ability to encapsulate several kinds of anticancer drugs such as PTX, curcumin, DOX, 6-Mercaptopurine, Vincristine, ADR, 5-FU among others, and deliver only them to the targeted tumour sites. Apart from these scientists in the recent time used chitosan for organ target drug delivery system which shows that chitosan has gained much importance in medical filed. The biomaterials used for tissue engineering requires specific properties such as biocompatibility, biodegradability, mucoadhesive, antibacterial and their degradation products must not be toxic, all of which are inherent for chitosan making it ideally suited as tissue engineering material. In addition, chitosan could be easily modified into scaffolds, hydrogels, nanofiber and dendrimer with additional properties as tissue engineering biomaterial. Chitosan scaffolds possess unique property to develop 3-dimentional environment for tissue engineering and use of different cross-linkers can help in degradation of shell material and drug release rate.

Chitosan has proven itself and promising encapsulating material suitable for various therapeutic agents like antithrombotic, anticancer, antibiotics, anti-inflammatory, proteins, and amino acids while insuring their effective bioavailability at the target sites with an additional advantage of control release. This allowed chitosan to gain attention not only in the medical field but also for extensive applications in all fields of science. Chitosan is an antimicrobial and antioxidant due to presence of amino groups which act as scavenger of free hydroxyl radicals and high degree of deacetylation also increase antioxidant property of chitosan. due to its antimicrobial and antioxidant activity chitosan has also been used in encapsulation of various food material to protect them from sever external environments including low pH. Chitosan encapsulation also mask smell and undesirable flavour of active ingredient and enhance the shelf life of food material. The antimicrobial activity of chitosan has made it a useful polymeric material for introducing antimicrobial properties in fibres. Encapsulation of various nanoparticles and anti-bacterial ingredients in chitosan and its application on fibres impart certain versatile properties such as antibacterial, mosquito repellent, durability, colour stability and fragrance finishing on fabrics.

4 Conclusions and future perspectives

Encapsulation involves the development of tiny capsule containing particular core material chitosan surrounded by shell which plays an important role in the slow release of some chemical. It has application in food, agriculture, cosmetics and pharmaceutical industries such as the development of new flavours, improving oil ingredients, like omega 3, with sugar beet pectin microencapsulated to replace milk proteins and gum arabic and improving oxidative stability. Chitosan encapsulation of active ingredients protects them from the surrounding environment for a specific time. Different techniques have been developed to encapsulate drugs, oils, haemoglobin and vaccines among other ingredients as a core material using chitosan as shell material through techniques such as emulsification, spray drying and coacervation. Encapsulated materials are released by different means, involving dissolution, melting or diffusion and rupture. Encapsulation involves an art and a science where experience is important to develop the required capsules. Charge, size, molecular weight and deacetylation level of chitosan have great effects on microcapsule developments. Chitosan has been widely used due to its non-toxic, biodegradable and biocompatible characteristics and novel applications in drug delivery and tissue engineering. Microencapsulation using chitosan has been effectively applied in the agriculture, cosmetics, food and pharmaceutical industries for encapsulating alcohols, aqueous solutions, oils and various other bioactives. Existing stimulant factors such as pH, enzyme activity, temperature, osmotic force and mechanical stress may rapidly or controllably release of drug from chitosan. In this situation, the release of encapsulated drug may control other stimulant like food constituent, water activity and microbial load. Heat stable encapsulating polymer quality will be needed in future for food industry because there is great challenge of survival of probiotics during heat treatment. Process cost and size of microcapsule must also be considered in future research.

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1071 **Table 1.** Physical properties of chitosan

Property	Indication	Reference
Solubility	Soluble in dilute aqueous acids, insoluble in water and organic solvents	[140]
Appearance	White powder or flakes	[141]
Molecular weight	Low MW- 50-190 kDa, ≥75% degree of deacetylation, 20-300 cPs.	[142]
	Medium MW- 190-310 kDa, 75-85% degree of deacetylation, 200-800 cPs.	
	High MW- 310-375 kDa, >75% degree of deacetylation, 800-2000 cPs.	
Colour	White	[141]
Odour	Odourless	[143]
Melting point	It depends on molecular weight	[144]
	Approximately 290°C	
Boiling point	Neither boil nor evaporate	[145]

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1074 **Table 2**. **Biological properties of chitosan**

Property	Applications	References
Antioxidant	Applicable in food and pharmaceutical industries	[146]
Antibacterial	Effective for biomedical purpose and agriculture	[147]
Antifungal	Used as antifungal agent in food	[148]
Antitumour	Used as chemotherapeutic agent against tumour for human	[149]
Biocompatible, biodegradable and nontoxic for normal constituent of body	For tissue engineering and artificial skin	[5]
Excellent Haemostatic potential	Important to stop bleeding	[150]
Immunoadjuvant	Effective to enhance immune system in human body	[151]
Wound healer and antiulcer agent	Biomedical industries	[152]
Effective drug delivery agent	Pharmaceutical agent	[153]

Important to accelerate osteoblast formation for bones	Applicable for the bone formation of human body	[154]
Mammalian and microbial cells easily bind to chitosan	Drug delivery and skin cells replacement	[155]
Effective pharmacological agent against hypercholesterolemia	Applicable to lower blood cholesterol level	[156]

Table 3. Some micro-encapsulation approaches along with their advantages and disadvantages

Encapsulation method	Advantages	Disadvantages	Reference
Spray drying	• High encapsulation efficiency • Stable encapsulated product • Cost effective • Applicable on industrial level • Easy to operate	• Difficult to control the particle size • Highly sensitive at high temperate • low yield for small batches	[157, 158]
Extrusion	• Prolong shelf life of products • Useful in temperature sensitive ingredients encapsulation • Shape of the extruded products can easily be controlled • Ingredients are truly encapsulated by wall material • Products are stable against oxidants	• Difficult of separate microcapsule form highly viscous polymeric solution. • Microcapsule must be separated from liquid bath • Low scale production	[159, 160]
Fluidized bed coating	• Economically efficient • Microcapsule size distribution is controllable	• Degrade the temperature sensitives active ingredients	[161, 162]

Freeze drying	• Stable products under oxidation conditions • Operate at low temperature • Suitable technique for the encapsulation of ingredients which are unstable in aqueous media.	• Process take too much time to complete • High energy input • Poor protection of ingredient due to porous covering. • Expensive technique	[157, 163]
Coacervation	• Useful for encapsulant of temperature sensitive actives • Organic solvent usage • Low cost • Applicable for large scale	• Presence of coacervating material on the surface of microcapsules • Complex process • Low stability for complex coacervates • Use of toxic chemical in the process • Expensive technique	[10, 15]
Emulsion	• Small diameter of microcapsules • Live cell can be encapsulated • Both hydrophobic and hydrophilic active	• Low thermal stability • Limited number of emulsifiers	[164, 165]

	ingredient can be encapsulated		
Liposome entrapment	• Used for encapsulation of both water and lipid soluble actives • Control sustained release of encapsulated ingredients • Deliver encapsulated content to right site at right time • Ingredients can be delivered across the membrane	• Expensive • Lap scale technique	[166, 167]
Spray cooling	• Useful for encapsulation of temperature sensitive active ingredient • Economically more efficient as compare to spray drying	• Low yield for small batches • Size of the particle is difficult to control • Required special condition for handling and storage of microcapsule	[168, 169]
In situ polymerization	• Inexpensive • Wall possess thermal resistance • Simple process and easy to operate	• Thickness of wall remain same for both large and small microcapsule.	[170, 171]

	• High loading core (up to 95%) • Resistance against harsh environment • Can be used at industrial level	• Formaldehyde a toxic compound is used in this process	
Solvent evaporation	• Simple process	• Low loading efficiency	[172, 173]

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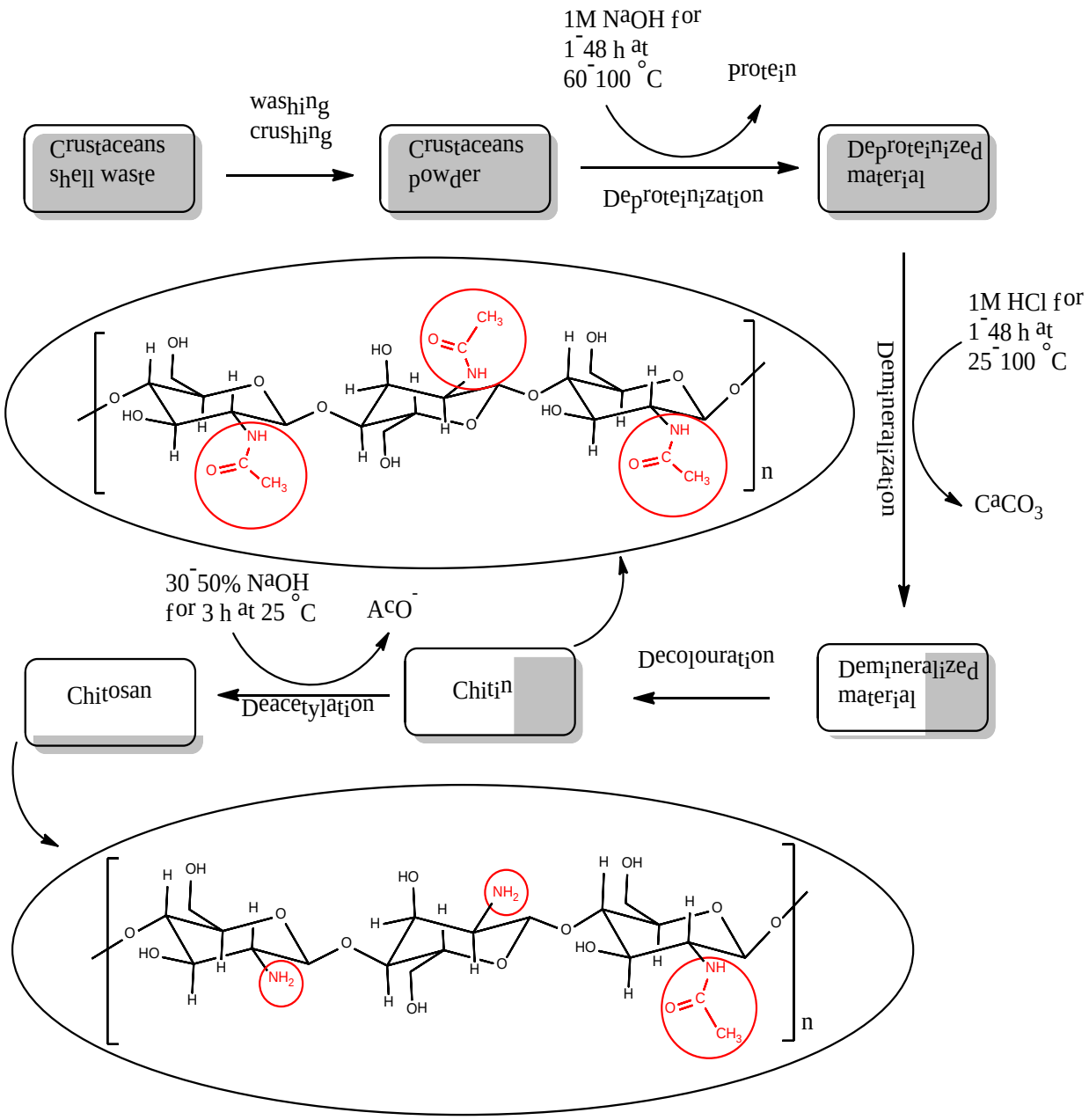
1094 **Table 4.** Chitosan encapsulation of various active ingredients for medical applications

Active agent(s)	Techniques	Applications	Reference
Lipophilic/hydrophobic drugs	Gelation and emulsification	Drug delivery in gastrointestinal tract	[5, 174]
Lipids (fats and oils)	Emulsification spray Drying	Controlling lipid digestion, preventing oxidation of oils	[44, 175]
Haemoglobin	Emulsification	Increased Oxygen affinity active transport of some proteins and lipids	[176]
α-lipoic acid	Spray drying	Antioxidant, Anti-inflammatory	[177]
Neem seed oil (NSO)	Complex coacervation	Pesticides, insecticide and herbicide	[178]
Astaxanthin	Emulsification	Antioxidant, used in aquaculture feed	[179]
Essential oils	Complex coacervation pad dry cure Method	Antibacterial, Antifungal, Aromatic textile finishing	[180]

Vaccines	Complex coacervation emulsification	Oral and nasal vaccine, immunity enhancement	[181] [182]
Quercetin	Spray drying	Antioxidant, anti-inflammatory anti-proliferative	[72]



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1113 **Fig. 1.** Illustration of chitin deacetylation in alkaline media for chitosan production

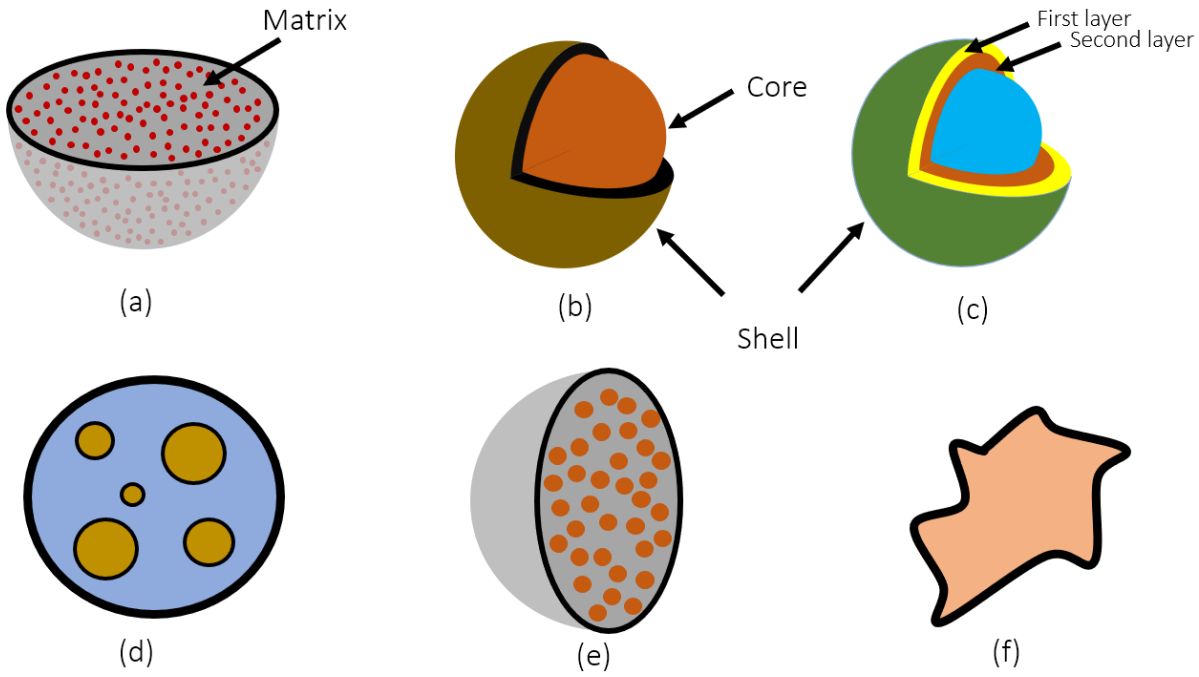

Fig. 2. Different forms of microcapsules (a) microparticles (b) single walled (c) multiwalled (d) multicore (e) microsphere (f) irregular microencapsule

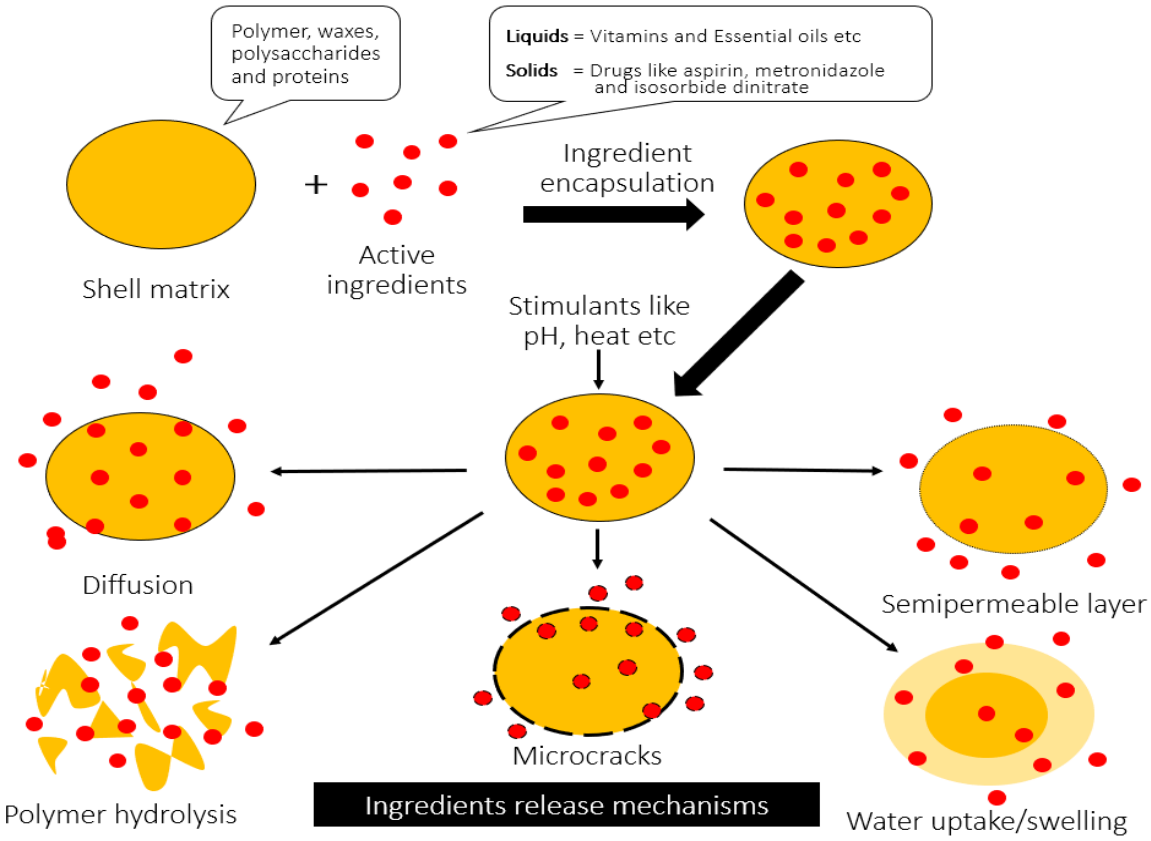

Fig. 3. Microencapsulation process and ingredients release mechanisms

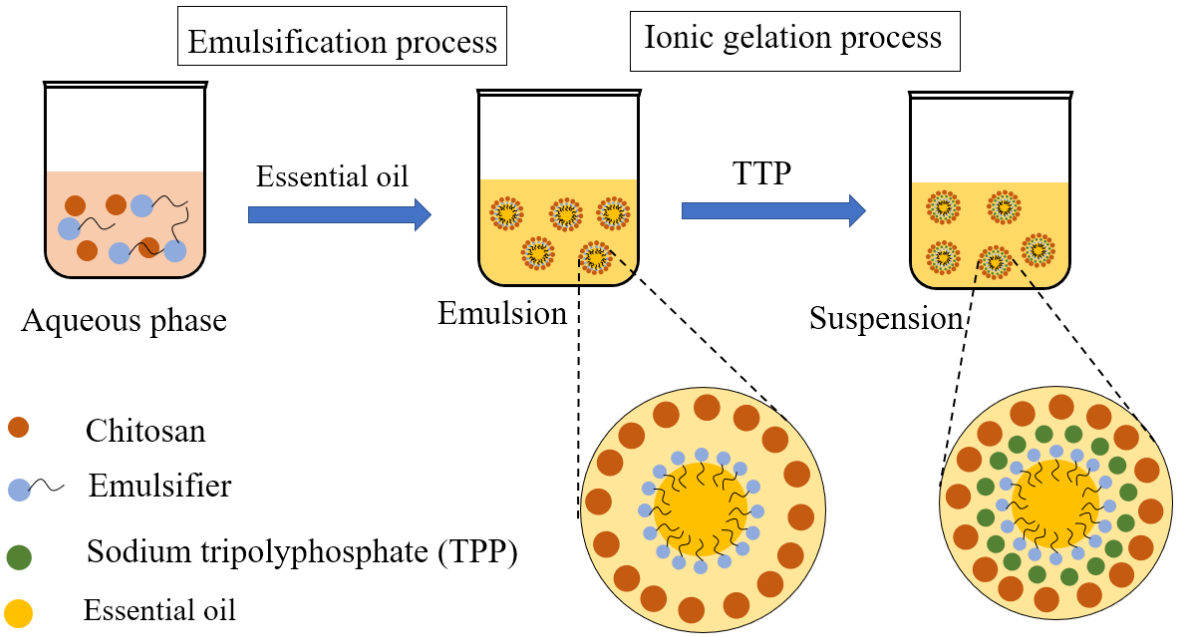

Fig. 4. Encapsulation of essential oil (EO) in chitosan through ionic gelation method

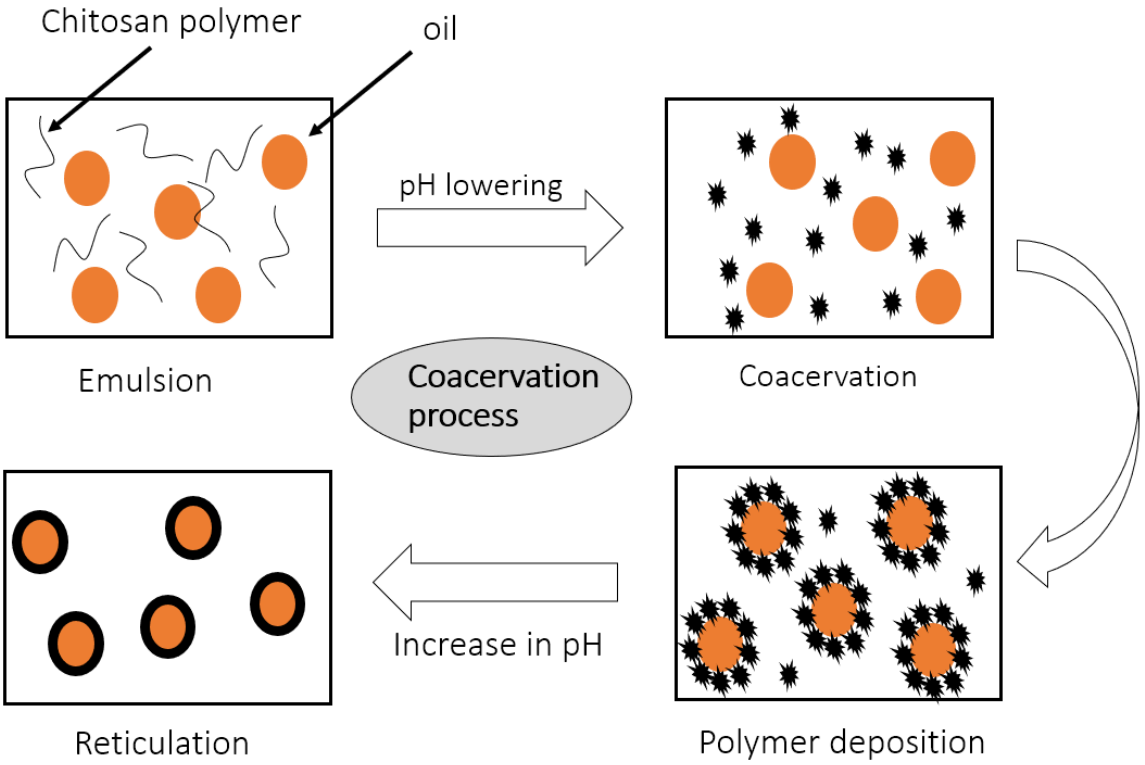

Fig. 5. Encapsulation of neem seed oil in chitosan through coacervation process

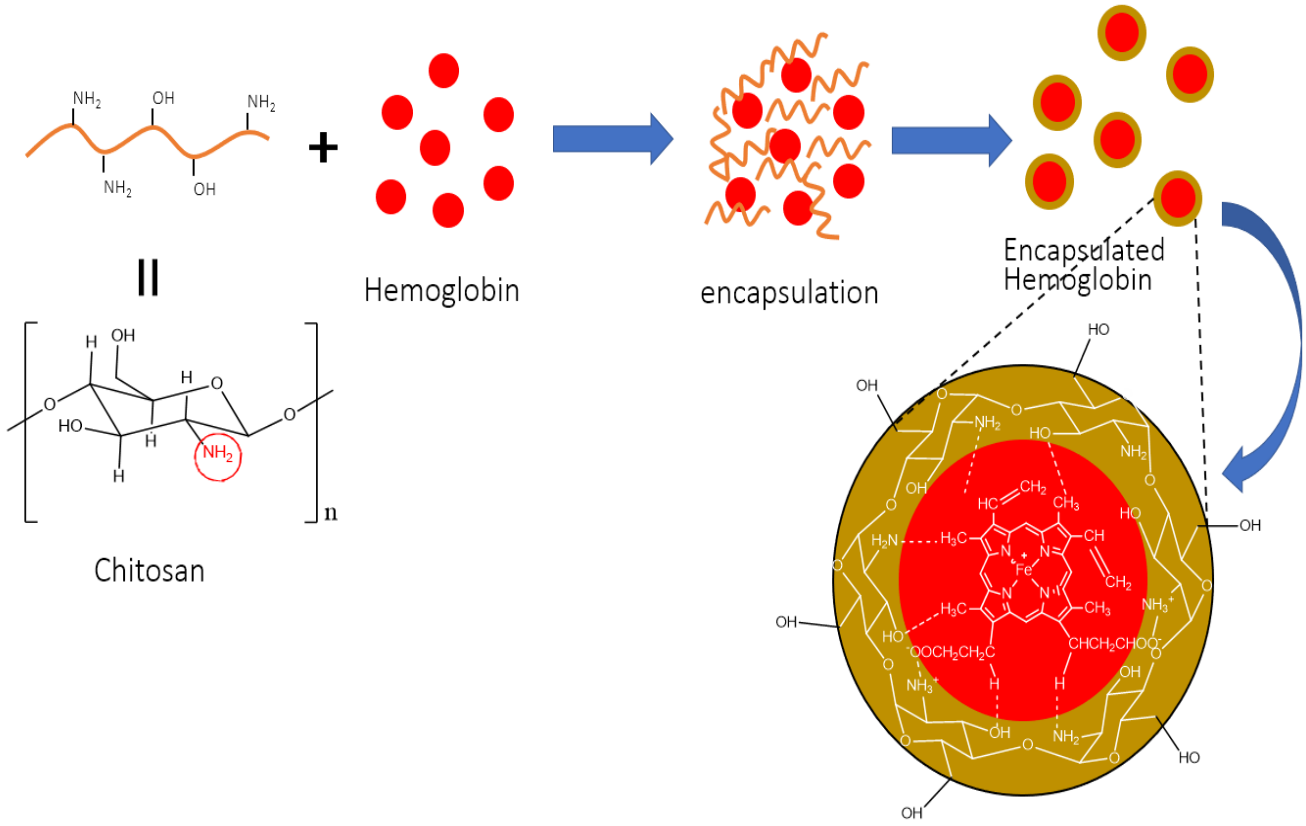

Fig. 6. Schematic representation of haemoglobin encapsulation in chitosan

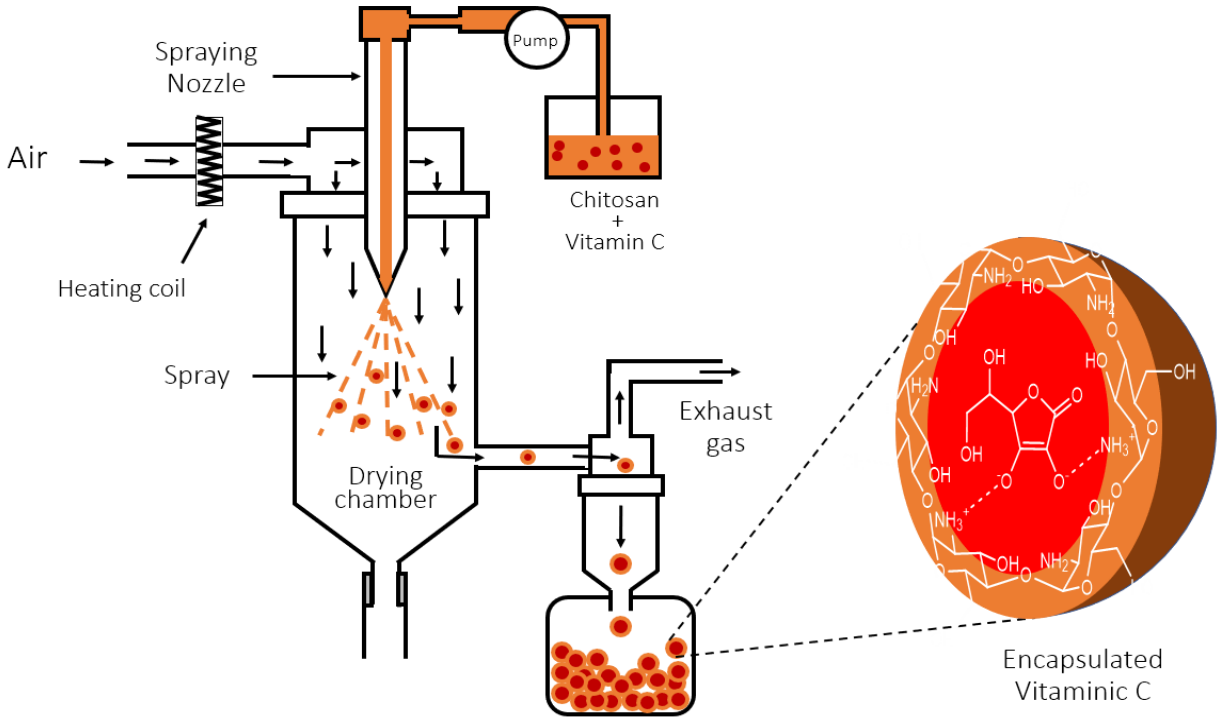

Fig. 7. Encapsulation of vitamin C in chitosan through spry drying method